

10/531,333

4 days resulted in suppression of testosterone to castrate levels, accompanied by an increase in the oral bioavailability of AG-045572 to 27%. In the same experiment, the male-specific pulsatile pattern of growth hormone remained unchanged, with slightly elevated basal levels. The potent GnRH receptor antagonist AG-045572 is metabolized by hormone-dependent CYP3A. As a result, suppression of testosterone by pretreatment with AG-045572 "feminized" its own pharmacokinetics.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L4 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:241135 CAPLUS

DOCUMENT NUMBER: 132:279106

TITLE: Non-peptide GnRH agents, methods and intermediates for

INVENTOR(S): their preparation
David Anderson, Mark Brian; Vazir, Haresh N.; Luthin,

P.; Robert; Paderes, Genevieve Deguzman; Pathak, Ved

Tompkins, Christie, Lance Christopher; Hong, Yufeng;

PATENT ASSIGNEE(S): Eileen Valenzuela; Li, Haitao; Faust, James
Agouron Pharmaceuticals, Inc., USA; et al.

SOURCE: PCT Int. Appl., 444 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020358	A2	20000413	WO 1999-US18790	19990820
WO 2000020358	A3	20001116		
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2341346	A1	20000413	CA 1999-2341346	19990820
BR 9913374	A	20010515	BR 1999-13374	19990820
EP 1105120	A2	20010613	EP 1999-968010	19990820
EP 1105120	B1	20050323		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			

10/531,333

HU 200103622	A2	20020429	HU 2001-3622	19990820
EE 200100102	A	20020617	EE 2001-102	19990820
SI 20746	A	20020630	SI 1999-20076	19990820
TR 200100631	T2	20020821	TR 2001-200100631	19990820
JP 2002535244	T	20021022	JP 2000-574479	19990820
AU 759310	B2	20030410	AU 2000-24709	19990820
NZ 509252	A	20040528	NZ 1999-509252	19990820
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NO 2001000309	A	20010411	NO 2001-309	20010119
IN 2001DN00066	A	20070112	IN 2001-DN66	20010124
ZA 2001000831	A	20020822	ZA 2001-831	20010130
MX 2001PA01834	A	20000821	MX 2001-PA1834	20010219
US 7101878	B1	20060905	US 2001-763216	20010220
LV 12732	B	20020320	LV 2001-45	20010316
BG 105362	A	20011231	BG 2001-105362	20010319
LT 4904	B	20020425	LT 2001-24	20010319
US 2004010033	A1	20040115	US 2003-353160	20030708
PRIORITY APPLN. INFO.:			US 1998-97520P	P 19980820
			WO 1999-US18790	W 19990820
			US 2001-763216	B3 20010220

OTHER SOURCE(S): MARPAT 132:279106

IT 263850-02-8P 263850-03-9P

RL: BAC (Biological activity or effector, except adverse); BSU

(Biological

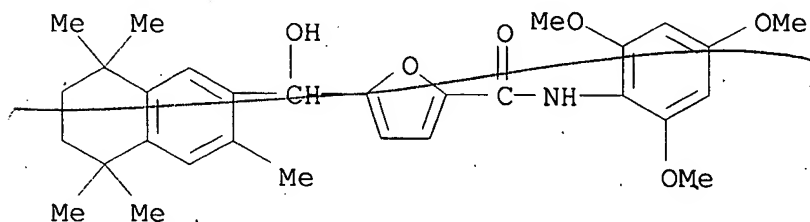
study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(comparison compound; preparation of non-peptide GnRH agents for regulating gonadotropin secretion)

RN 263850-02-8 CAPLUS

CN 2-Furancarboxamide,

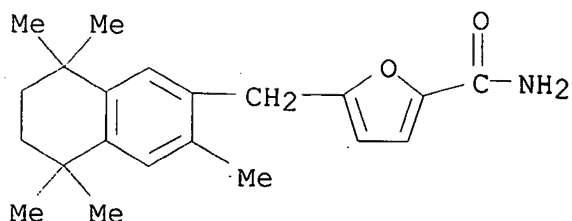
5-[hydroxy(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-N-(2,4,6-trimethoxyphenyl)- (9CI) (CA INDEX NAME)



RN 263850-03-9 CAPLUS

CN 2-Furancarboxamide, 5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

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IT 263878-35-9P

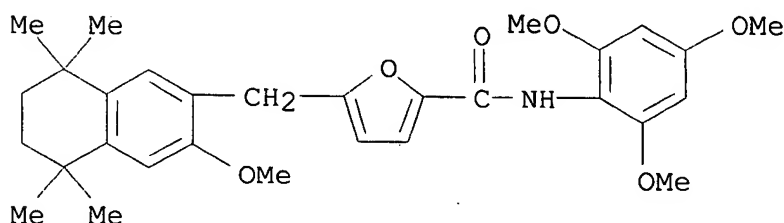
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of non-peptide GnRH agents for regulating gonadotropin secretion)

RN 263878-35-9 CAPLUS

CN 2-Furancarboxamide,

5-[(5,6,7,8-tetrahydro-3-methoxy-5,5,8,8-tetramethyl-2-naphthalenyl)methyl]-N-(2,4,6-trimethoxyphenyl)- (9CI) (CA INDEX NAME)



IT 263848-89-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

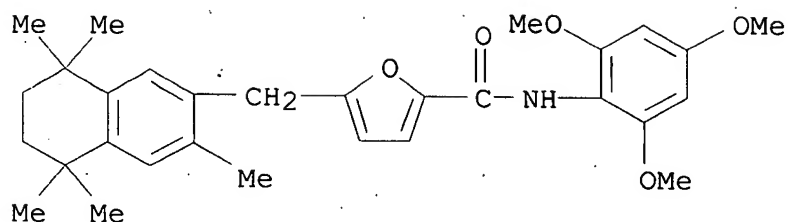
study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(target compound; preparation of non-peptide GnRH agents for regulating gonadotropin secretion)

RN 263848-89-1 CAPLUS

CN 2-Furancarboxamide, N-[[3-(aminomethyl)phenyl]methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

10/531,333

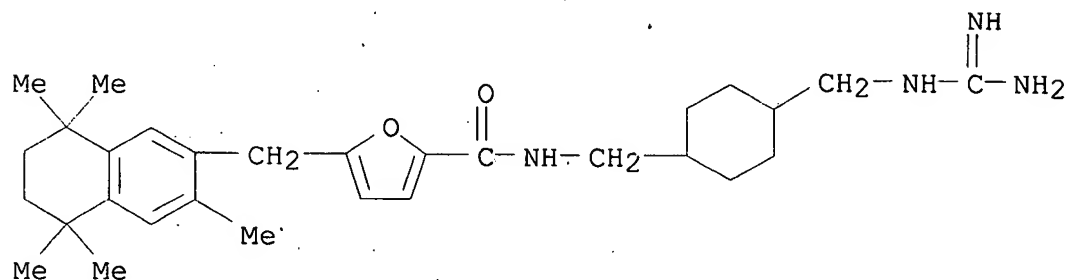


RN 263847-61-6 CAPLUS

CN 2-Furancarboxamide,

N-[[4-[[[(aminoiminomethyl)amino)methyl]cyclohexyl]meth

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(9CI) (CA INDEX NAME)

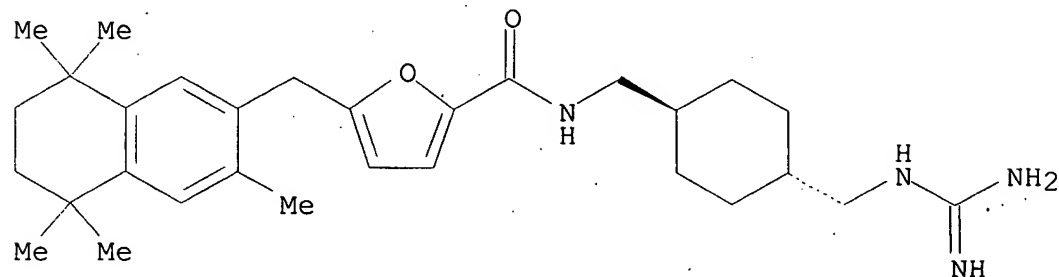


RN 263847-62-7 CAPLUS

CN 2-Furancarboxamide,

N-[[trans-4-[[[(aminoiminomethyl)amino)methyl]cyclohexyl]
methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-
naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

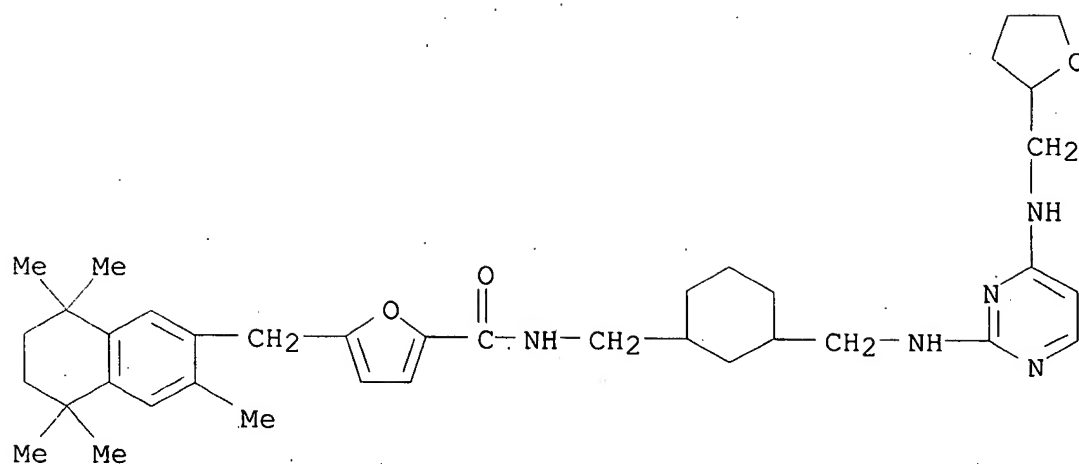
Relative stereochemistry.



RN 263847-63-8 CAPLUS

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3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

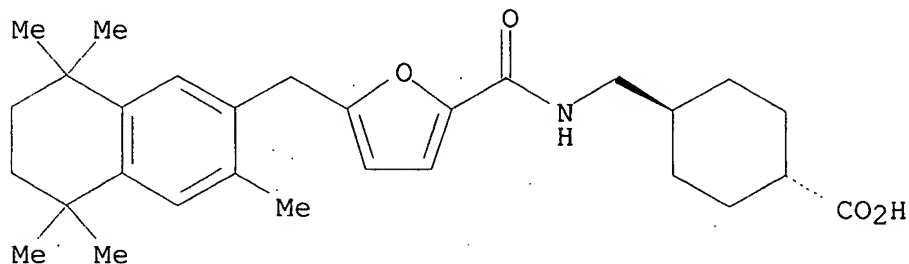
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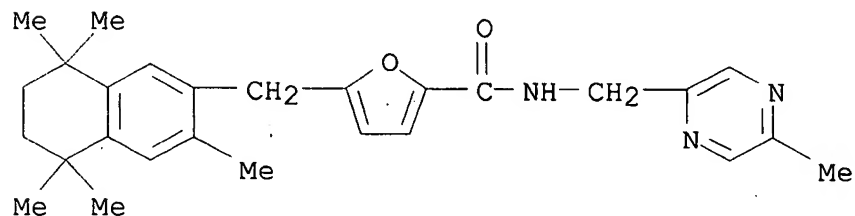
CN Cyclohexanecarboxylic acid, 4-[[[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-2-furanyl]carbonyl]amino]methyl]-, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 263847-65-0 CAPLUS

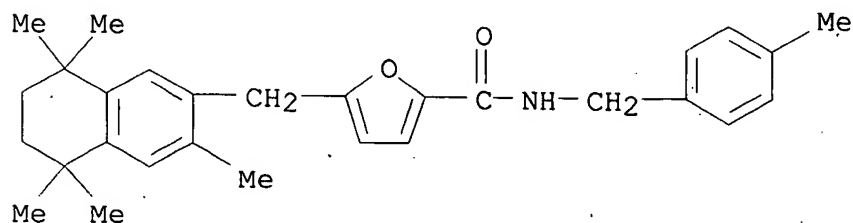
CN 2-Furancarboxamide, N-[(5-methylpyrazinyl)methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



RN 263847-66-1 CAPLUS

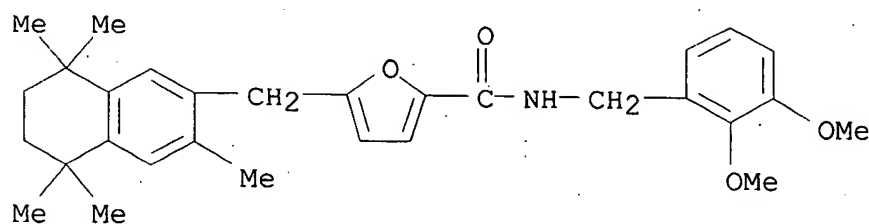
10/531,333

CN 2-Furancarboxamide, N-[(4-methylphenyl)methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (CA INDEX NAME)



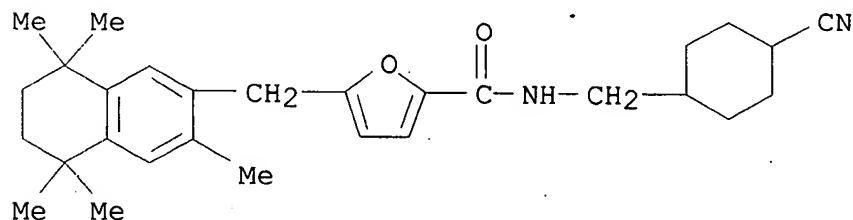
RN 263847-67-2 CAPLUS

CN 2-Furancarboxamide,
N-[(2,3-dimethoxyphenyl)methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



RN 263847-68-3 CAPLUS

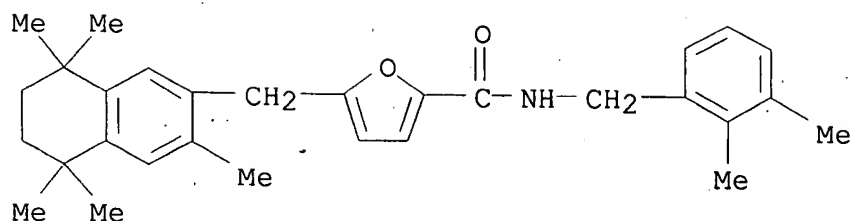
CN 2-Furancarboxamide,
N-[(4-cyanocyclohexyl)methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



RN 263847-69-4 CAPLUS

CN 2-Furancarboxamide,
N-[(2,3-dimethylphenyl)methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

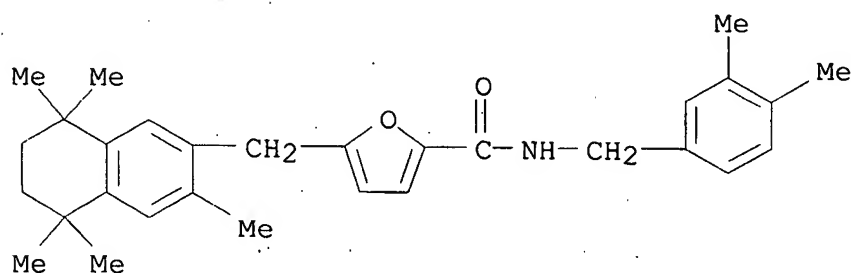
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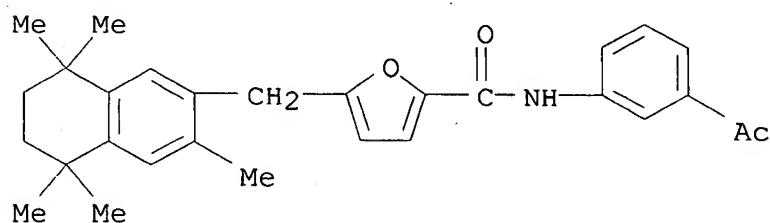
N-[(3,4-dimethylphenyl)methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



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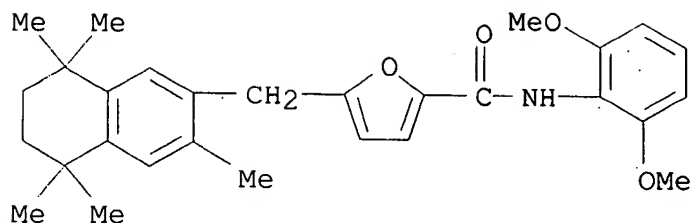
N-(3-acetylphenyl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



RN 263847-72-9 CAPLUS

CN 2-Furancarboxamide, N-(2,6-dimethoxyphenyl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

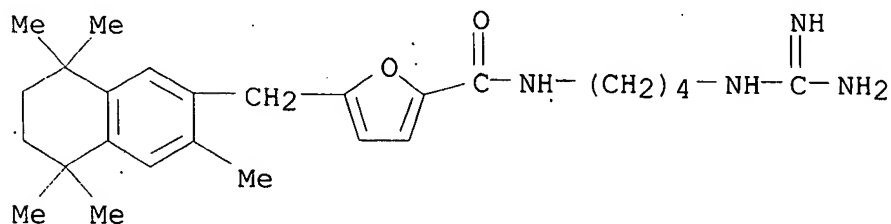
10/531,333



RN 263847-73-0 CAPLUS

CN 2-Furancarboxamide, N-[4-[(aminoiminomethyl)amino]butyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA

INDEX
NAME)

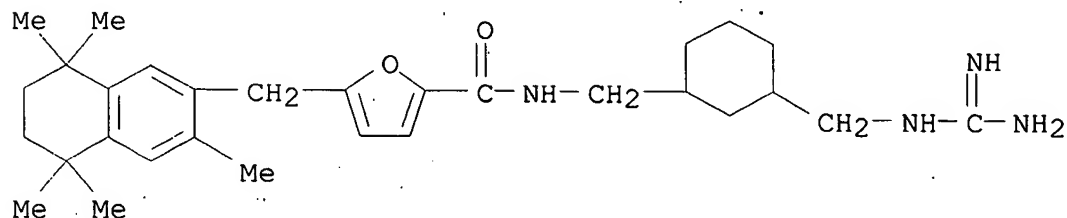


RN 263847-74-1 CAPLUS

CN 2-Furancarboxamide,

N-[[3-[[[(aminoiminomethyl)amino]methyl]cyclohexyl]meth

yl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
(9CI) (CA INDEX NAME)



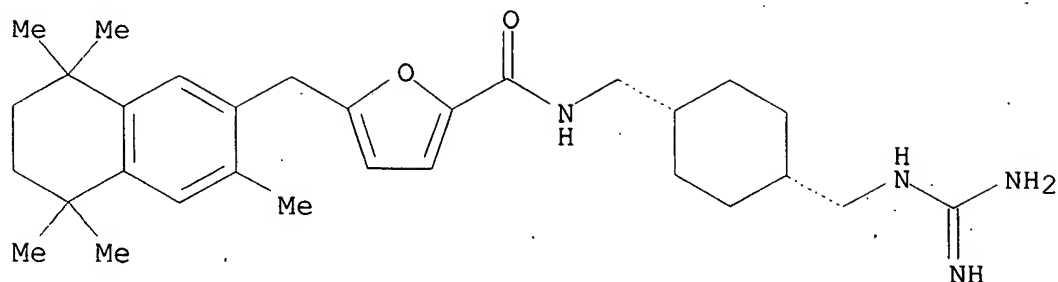
RN 263847-75-2 CAPLUS

CN 2-Furancarboxamide,

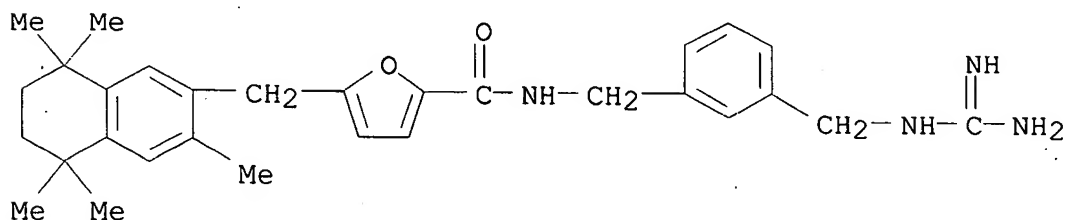
N-[[cis-4-[[[(aminoiminomethyl)amino]methyl]cyclohexyl]
methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-
naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

Relative stereochemistry.

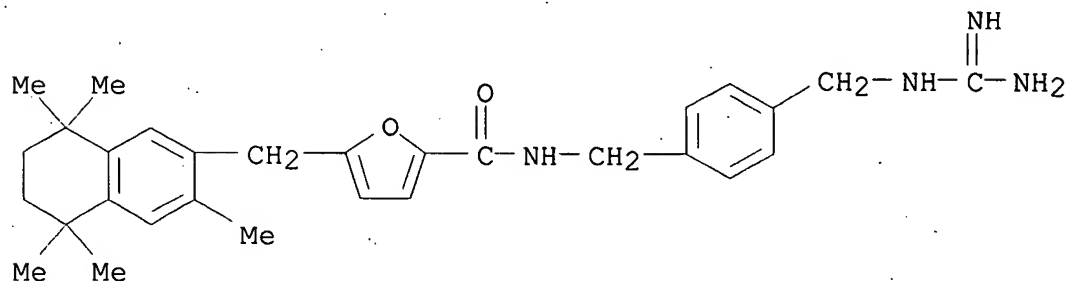
10/531,333



RN 263847-76-3 CAPLUS
 CN 2-Furancarboxamide,
 N-[[3-[[[(aminoiminomethyl)amino]methyl]phenyl]methyl]-
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 (9CI)
 (CA INDEX NAME)



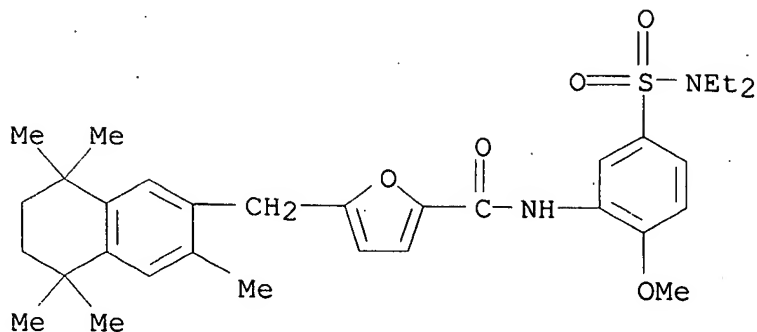
RN 263847-77-4 CAPLUS
 CN 2-Furancarboxamide,
 N-[[4-[[[(aminoiminomethyl)amino]methyl]phenyl]methyl]-
 5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
 (9CI)
 (CA INDEX NAME)



RN 263847-78-5 CAPLUS
 CN 2-Furancarboxamide, N-[5-[(diethylamino)sulfonyl]-2-methoxyphenyl]-5-
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 (9CI)

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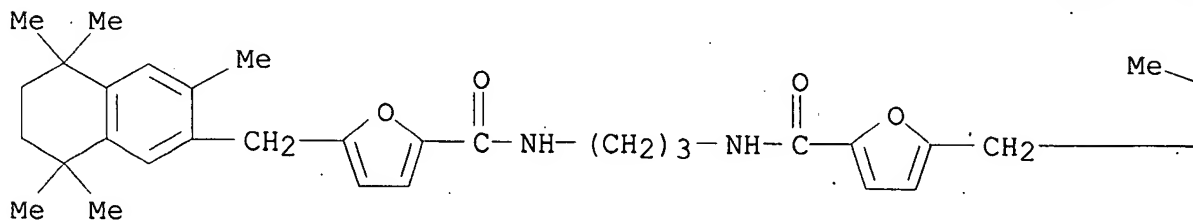
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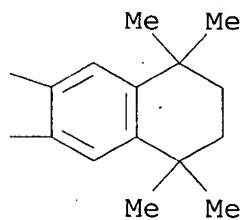
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CN 2-Furancarboxamide, N,N'-1,3-propanediylbis[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



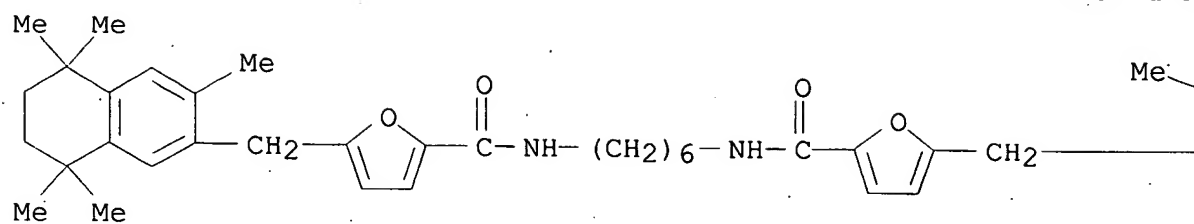
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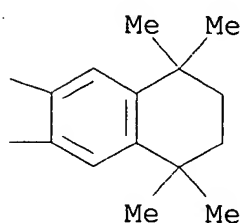
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CN 2-Furancarboxamide, N,N'-1,6-hexanediylbis[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



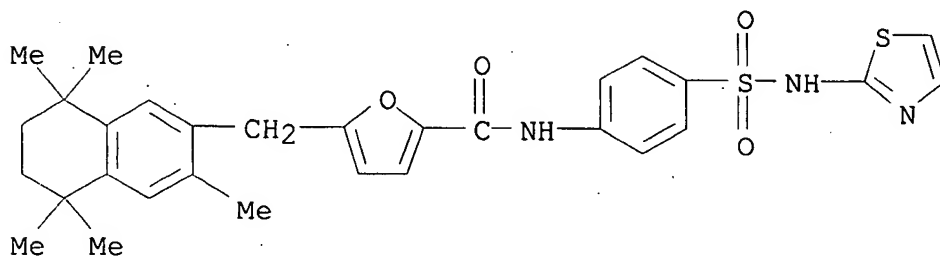
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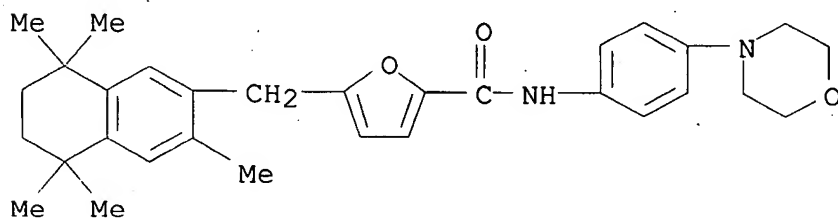
CN 2-Furancarboxamide, 5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-N-[4-[(2-thiazolylamino)sulfonyl]phenyl]- (9CI)

(CA INDEX NAME)



RN 263847-82-1 CAPLUS

CN 2-Furancarboxamide, N-[4-(4-morpholinyl)phenyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

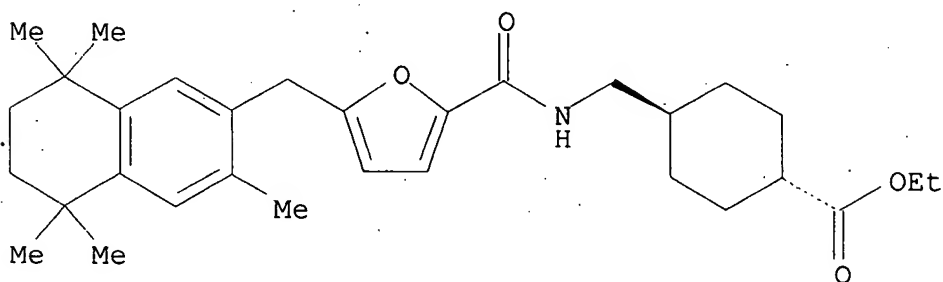


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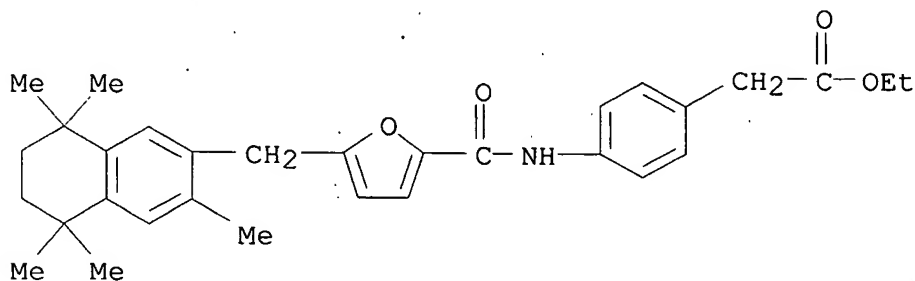
CN Cyclohexanecarboxylic acid, 4-[[[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-2-furanyl]carbonyl]amino]methyl]-, ethyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



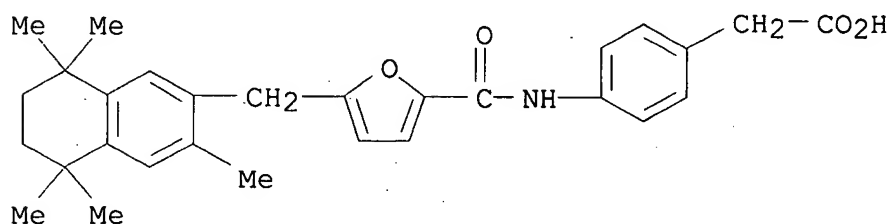
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CN Benzeneacetic acid, 4-[[[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-2-furanyl]carbonyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)



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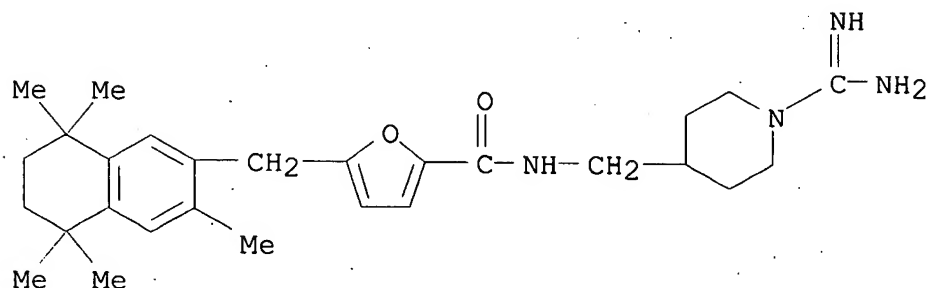
CN Benzeneacetic acid, 4-[[[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-2-furanyl]carbonyl]amino]- (9CI) (CA INDEX NAME)



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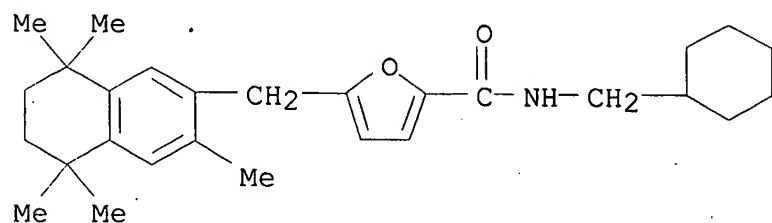
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CN 2-Furancarboxamide, N-[[1-(aminoiminomethyl)-4-piperidinyl]methyl]-5-
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(9CI)
(CA INDEX NAME)



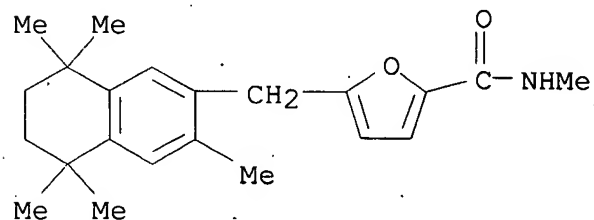
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CN 2-Furancarboxamide,
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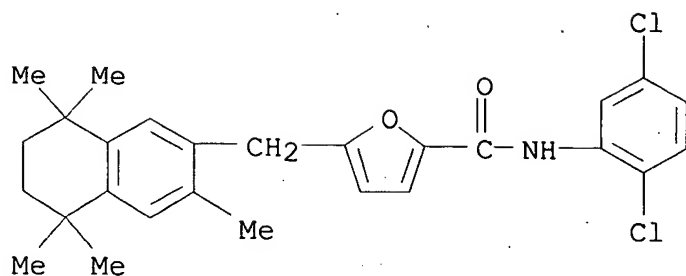
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N-methyl-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-
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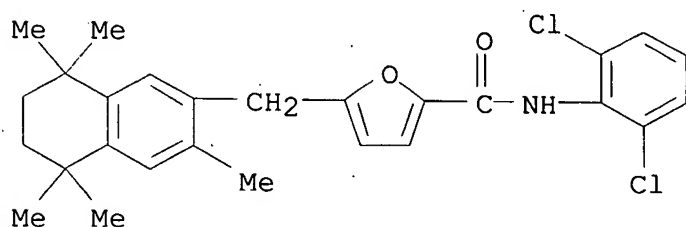
CN Hexanoic acid, 6-[[[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-
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(CA

10/531,333



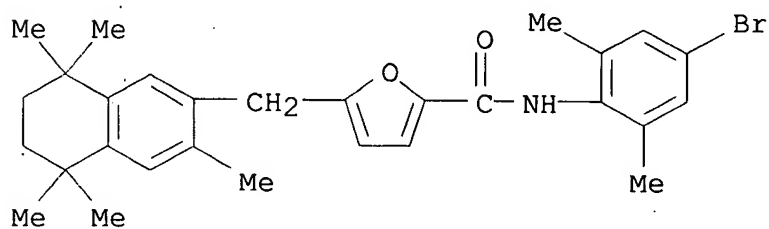
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CN 2-Furancarboxamide, N-(2,6-dichlorophenyl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



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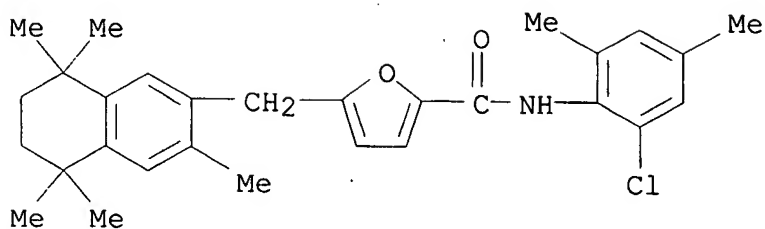
CN 2-Furancarboxamide, N-(4-bromo-2,6-dimethylphenyl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



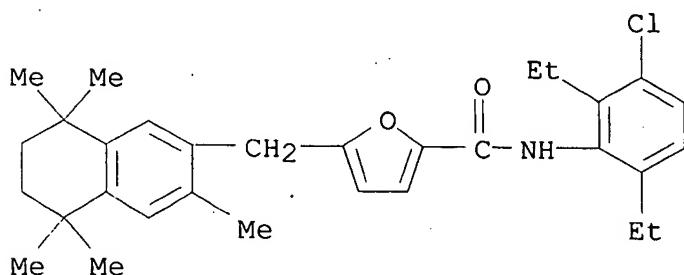
RN 263858-09-9 CAPLUS

CN 2-Furancarboxamide, N-(2-chloro-4,6-dimethylphenyl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

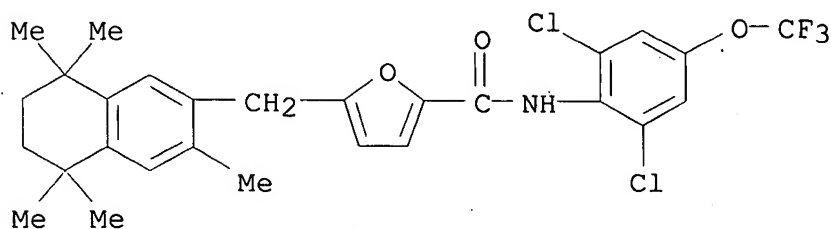
10/531,333



RN 263858-10-2 CAPLUS
CN 2-Furancarboxamide,
N-(3-chloro-2,6-diethylphenyl)-5-[(5,6,7,8-tetrahydro-
3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

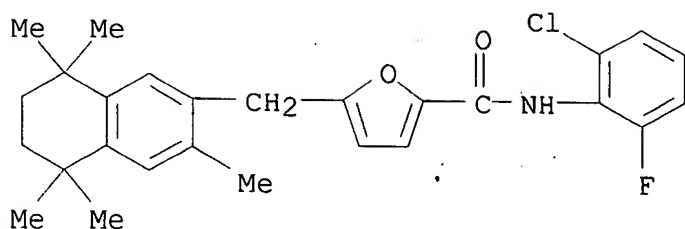


RN 263858-11-3 CAPLUS
CN 2-Furancarboxamide, N-[2,6-dichloro-4-(trifluoromethoxy)phenyl]-5-
[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
(9CI)
(CA INDEX NAME)



RN 263858-12-4 CAPLUS
CN 2-Furancarboxamide, N-(2-chloro-6-fluorophenyl)-5-[(5,6,7,8-tetrahydro-
3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

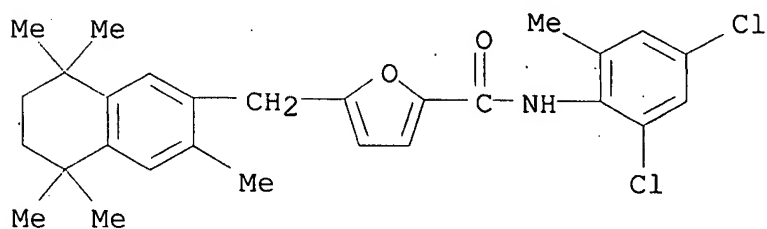
10/531,333



RN 263858-13-5 CAPLUS

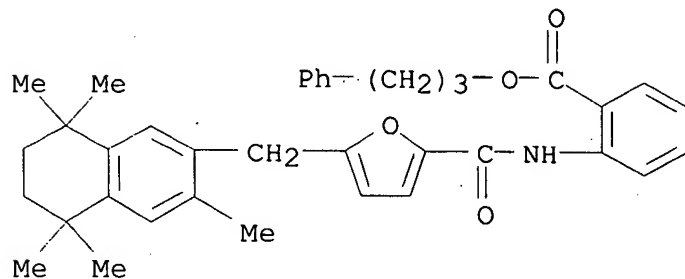
CN 2-Furancarboxamide,

N-(2,4-dichloro-6-methylphenyl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



RN 263858-14-6 CAPLUS

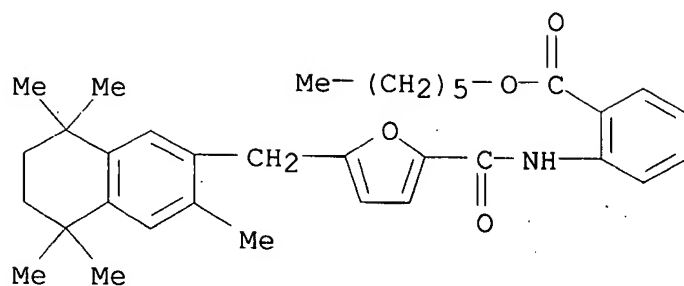
CN Benzoic acid, 2-[[[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-2-furanyl]carbonyl]amino]-, 3-phenylpropyl ester (9CI) (CA INDEX NAME)



RN 263858-15-7 CAPLUS

CN Benzoic acid, 2-[[[5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-2-furanyl]carbonyl]amino]-, hexyl ester (9CI) (CA INDEX NAME)

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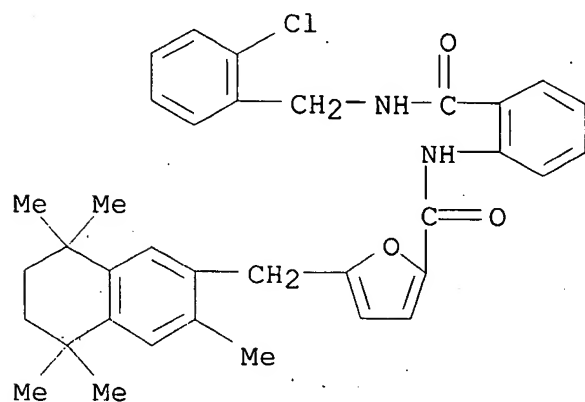
RN 263858-16-8 CAPLUS

CN 2-Furancarboxamide,

N-[2-[[[(2-chlorophenyl)methyl]amino]carbonyl]phenyl]-

5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
(9CI)

(CA INDEX NAME)



RN 263858-17-9 CAPLUS

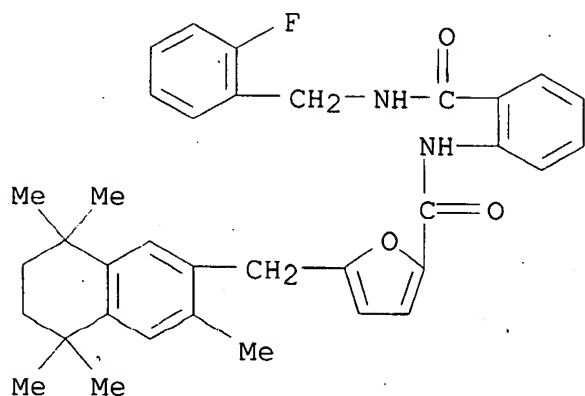
CN 2-Furancarboxamide,

N-[2-[[[(2-fluorophenyl)methyl]amino]carbonyl]phenyl]-

5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
(9CI)

(CA INDEX NAME)

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RN 263858-18-0 CAPLUS

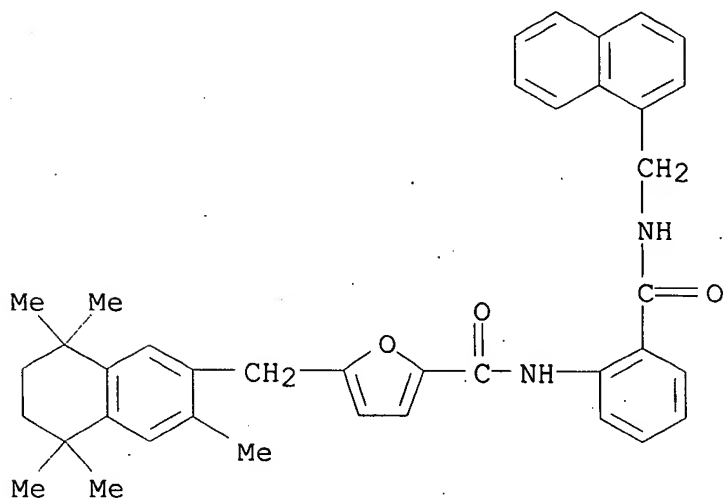
CN 2-Furancarboxamide,

N-[2-[[(1-naphthalenylmethyl)amino]carbonyl]phenyl]-5-

[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-

(9CI)

(CA INDEX NAME)



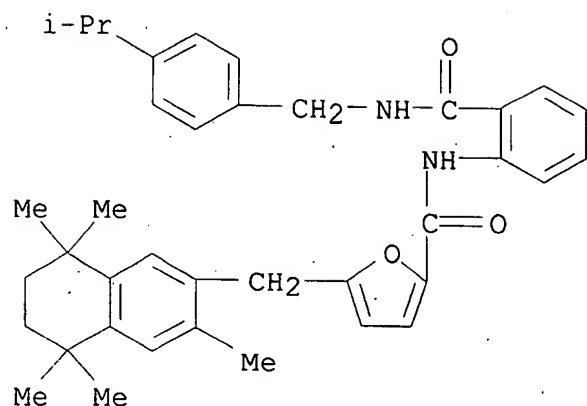
RN 263858-19-1 CAPLUS

CN 2-Furancarboxamide,

N-[2-[[[4-(1-methylethyl)phenyl]methyl]amino]carbonyl

]phenyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)

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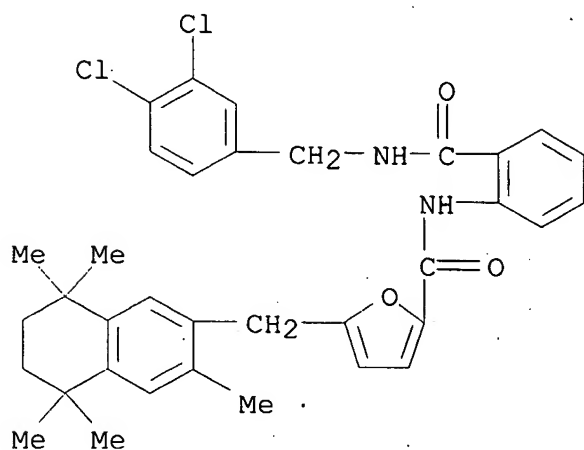


RN 263858-20-4 CAPLUS

CN 2-Furancarboxamide,

N-[2-[[[(3,4-dichlorophenyl)methyl]amino]carbonyl]phen

yl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
(9CI) (CA INDEX NAME)



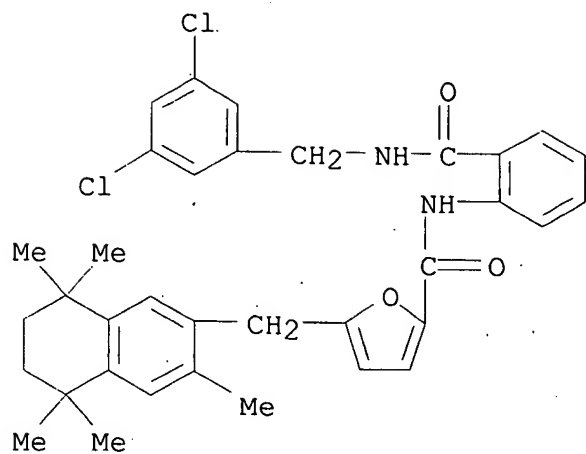
RN 263858-21-5 CAPLUS

CN 2-Furancarboxamide,

N-[2-[[[(3,5-dichlorophenyl)methyl]amino]carbonyl]phen

yl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
(9CI) (CA INDEX NAME)

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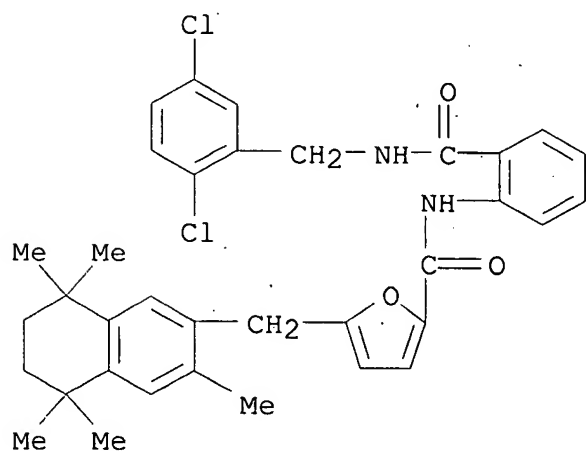


RN 263858-22-6 CAPLUS

CN 2-Furancarboxamide,

N-[2-[[[(2,5-dichlorophenyl)methyl]amino]carbonyl]phen

yl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
(9CI) (CA INDEX NAME)



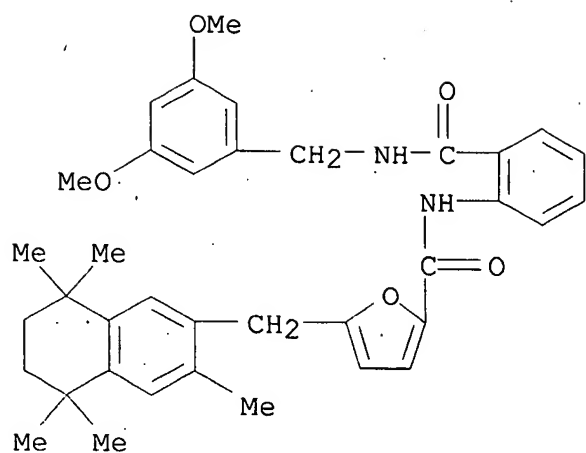
RN 263858-23-7 CAPLUS

CN 2-Furancarboxamide,

N-[2-[[[(3,5-dimethoxyphenyl)methyl]amino]carbonyl]phe

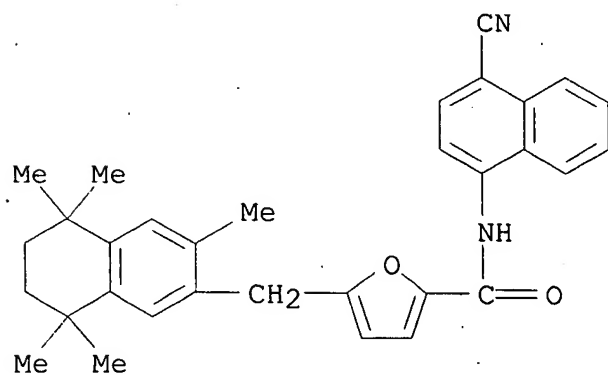
nyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]-
(9CI) (CA INDEX NAME)

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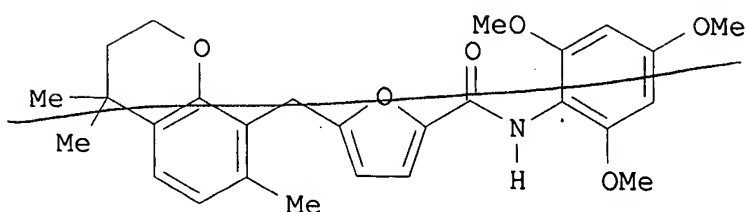
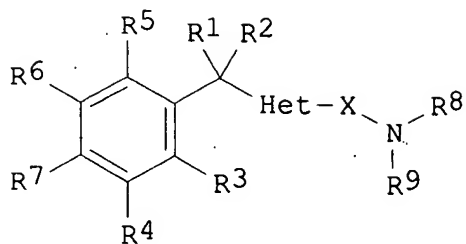


RN 263858-24-8 CAPLUS

CN 2-Furancarboxamide, N-(4-cyano-1-naphthalenyl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME).



GI



AB Non-peptide GnRH agents capable of inhibiting the effect of gonadotropin-releasing hormone are described. The compds. and their pharmaceutically acceptable salts, multimers, prodrugs, and active metabolites are suitable for treating mammalian reproductive disorders and steroid hormone-dependent tumors as well as for regulating fertility, where suppression of gonadotropin release is indicated. The compds. include those of formula I [X = C:O, C:S, S:O, or SO₂; Het = 5-membered NOS-heterocycle; R₁, R₂ = H, alkyl; R₃-R₇ = H, halo, (un)substituted alkyl, aryl, heteroaryl, CH₂OR, OR, CO₂R; R = alkyl, aryl, etc.; adjacent rings positions such as R₆R₇ may form (un)substituted 5- or 6-membered ring with up to 4 heteroatoms; R₈ = lipophilic moiety such as alkyl, aryl, CH₂OR, OR, etc.; R₉ = H, (un)substituted alkyl]. Methods and intermediates for synthesizing the compds. are also described. For instance, 4,4,7-trimethylchroman (preparation given) was alkylated in the 6- and 8-positions using Et 5-(chloromethyl)-2-furoate (46% total yield), and the resulting esters were hydrolyzed to a mixture of acids. This unsepd. mixture was treated with SOCl₂ and amidated with 2,4,6-trimethoxyphenylamine-HCl to give the invention compound II and its chroman-6-position isomer, which were separated by HPLC. Several compds. exhibited high affinity (<100 nM) at human GnRH receptors. The compds. antagonized GnRH-stimulated

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inositol phosphate accumulation in cells with recombinant human GnRH receptors, and an example compound reduced plasma LH levels in castrated male rats. Various biol. data for several hundred compds. are given.

=> log y

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
54.58	226.89

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-7.80	-7.80

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STN INTERNATIONAL LOGOFF AT 13:56:55 ON 10 AUG 2007